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Key questions for the future of amyloid research in dementia: a framework for integrating complex datasets

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Alzheimer's disease research is moving into a new era, yet significant questions remain about its underlying biological mechanisms. In this article, we consider how the field might refine the transfer of evidence between research cohorts focused on rare, genetically defined familial forms of dementia, clinical trial cohorts, highly selective of relatively younger people, with single neuropathologies and few co-morbidities, and the overall picture of the dementia syndrome in the whole population. We examine four key areas in which the evidence base must be improved: i) how 'disease' definitions apply across these three groups, ii) the precise molecular identification of the protein at the heart of current Alzheimer's research - amyloid beta protein, iii) the contributions of the full amyloid precursor protein proteolytic system and iv) how this complex proteolytic system relates to wider cellular systems. We describe how a cross-disciplinary approach based on the APP matrix framework, could allow a systematic investigation of new perspectives to inform translational research and precision medicine approaches. Addressing these gaps will give us the biological grounding needed to provide a sound underpinning to innovations in the field.

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INTRODUCTION

The reductions in the rate of cognitive decline reported in recent trials of amyloid immunotherapy, using a variety of monoclonal antibodies as therapeutic interventions for early Alzheimer's disease (AD) [1, 2], have attracted critique and acclaim in varying measure. Outstanding issues include: the clinical meaningfulness of observed reductions over the short [3] and long terms [4]; the scale of side effects [3, 5], the practicalities of determining eligibility and delivery [6], costs versus benefits [7, 8] and unblinding [9, 10]. Participants in the trials have experienced a variety of side effects including amyloid related imaging abnormalities (ARIA) involving brain oedema (ARIA-E) and haemorrhage (ARIA-H) as well as accelerated brain atrophy [11, 12]. In combination, these issues raise significant obstacles to routine use of anti-amyloid immunotherapy in the general population [8].

The anti-amyloid trials are the culmination of over 30 years of research based on the amyloid cascade hypothesis [13], the dominant hypothesis proposed to account for disease pathways in AD. This hypothesis describes disease pathways in which increased levels of "neurotoxic" amyloid-beta protein (Aβ), particular forms of Aβ aggregation, or a reduced the Aβ42:Aβ40 ratio, are proposed to trigger a cascade of changes that lead to a dementia syndrome; thus removal of Aβ should halt disease progression, provided it is initiated early enough, that clearance is sufficient, and there are no other pathologies present which can lead to (non-AD) dementia [14, 15]. Human early-onset dementia is associated with mutations in genes i) *AβPP* encoding the amyloid precursor protein (APP) and ii) the presenilin (PS) genes *PS1* and *PS2* encoding presenilin proteins 1 and 2 that form part of the γ-secretase complex involved in cleavage of APP, and the association of dementia with Down syndrome with three copies of the *AβPP* gene on chromosome 21 [16] - all of which are thought to increase Aβ, have underpinned this hypothesis.

Evidence from brain imaging [17–20], and biomarkers from biological fluids [21, 22], showing that increasing amyloid deposition generally precedes other neuropathological changes [23] and cognitive decline, have added further support and indeed have been used to monitor progression in clinical trials. Genetic and biomarker evidence, coupled with neuropathological evidence of the deposition of aggregated Aβ in plaques and in blood vessels, in the brains of people dying with dementia, has meant that this hypothesis has dominated dementia research. Contradicting this, studies investigating genetically defined AD have shown that rather than increasing Aβ production, the majority of mutations in the gene encoding PS1 lead to a reduction in Aβ production [24], with only 10% of the mutations studied showing a reduced Aβ42:Aβ40 ratio [25]. Additionally, lower, not higher, γ-secretase activities from specific mutations in *PSEN1* are associated with faster amyloid accumulation seen with PiB-PET signal and more rapid atrophy of the hippocampus [26].

The amyloid cascade hypothesis has never been fully accepted by the entire dementia research community. Evidence from population-representative and community studies of the older population [27, 28] highlights the complex, multifactorial nature of the dementia syndrome, with contributions from wide ranging in-life factors such as age [29], comorbidities [30], education [31, 32] physical activity [33] and gender [34]. A range of neuropathologies

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co-occur with the widely accepted neuropathological hallmarks of dementia, amyloid plaques and neurofibrillary tangles [35–39], and are associated with dementia [40]. These include atrophy [41], gliosis [42], neuronal loss - including hippocampal sclerosis [43, 44], pathology associated with the transactive response element DNA binding protein of 43 kDa (TDP-43) [45], Lewy bodies [40] and a range of vascular features [46–48]. In these studies, pathologies diagnostic for dementia are associated with the risk of developing dementia, but do not define it, due to their strong associations with age and a variety of other factors [27, 35, 36, 49]. Dementia in the population is rarely the "pure" AD associated with early-onset familial forms. Most people in the general population with asymptomatic amyloid neuropathology will not develop dementia in their lifetime [50]. Rather, increasing numbers of different pathologies are associated with an increased risk of dementia [27, 28]. We cannot yet reliably predict who in the ageing population will go on to develop dementia later in life in those with asymptomatic Alzheimer-related neuropathological changes [50], or those diagnosed with 'mild cognitive impairment' [51–53].

Dementia can be seen as a highly complex clinical syndrome [54] for which our biological understanding of the underlying pathological mechanisms remains incomplete. It is increasingly acknowledged that the complexity of the dementia syndrome underlies the difficulties in identifying and developing single-target therapeutic interventions [55, 56].

AD research is entering a new phase where investments (e.g. the UK Dementia Research Institutes and the ARUK Drug Discovery Alliance) are widening the research focus to other dementia associated factors as well as research to refine the understanding of the role(s) of amyloid in dementia. Here we examine what practical steps are needed to achieve this refinement by re-assessing evidence from a basic science perspective to identify evidence gaps in four key areas. For each, we establish where current research strategies leave some important aspects unaddressed and suggest practical measures to improve the evidence base.

GAP 1 – DISEASE DEFINITION AND MISMATCH BETWEEN RESEARCH, CLINICAL TRIAL AND REAL-WORLD POPULATIONS

There are many ways to define Alzheimer's type dementia depending on research perspective.

I. Familial, early-onset, AD is defined qualitatively by the possession of specific, fully-penetrant mutations in the genes encoding APP and PS1, duplication of the *AβPP* gene or for some, PS2 mutations.
II. AD neuropathological change (ADNC) [57] based on deposition of Aβ as amyloid plaques and the microtubule associated protein Tau as tangles and neuritic plaques, with or without consideration of cognitive status, attempts to define dementia neuropathologically across different dementia groups to reflect its biological components.
III. Clinically, AD is diagnosed by cognitive impairments that affect activities in daily life. The clinical diagnosis of possible or probable Alzheimer's disease can be supported by clinical trajectory, absence of major vascular disease and evidence from imaging or biomarkers [58] and is confirmed after death by neuropathological assessment [59, 60].

For sporadic, late onset dementia, particularly those in the oldest old age groups (where dementia is most common), the associations between dementia and pathology are complex [37], and there is no consistent, defining biological feature of dementia. Instead, 'disease' is described by cognitive status and assessments of activities of daily living, increasingly in conjunction with binary cut-offs in levels of brain imaging [17–20], and biological fluids based [21, 22] biomarkers which estimate neuropathological accumulation. Diagnoses are confirmed by neuropathological assessment after death [59, 60]. For the majority of those with dementia in the older population, diagnoses of AD based on clinical features correspond only moderately with the neuropathology seen at death in population-based clinicopathological studies [28, 35, 36, 57]. Similar associations can be seen in imaging studies, e.g. ~31% of those with clinically diagnosed possible or probable AD did not have raised amyloid deposition based on the florbetapir scan interpretation [61].

Physical comorbidities such as frailty [62–64], hypertension [65], diabetes mellitus [66] and hypercholesterolemia [67, 68] are common in older people and associated with dementia in addition to Alzheimer disease associated neuropathological changes [69]. These comorbidities may partly explain why only 8% of those with a diagnosis of 'early AD' in the Mayo Clinic Study of Aging (itself a semi-selective sample) would have been eligible for inclusion in a clinical trial for Lecanemab due to inclusion criteria such as increased amyloid on PiB PET and exclusion criteria such as those with various comorbidities or possession of the Apolipoprotein Eε4 allele [70]. Clinical trial participants using diagnostic criteria that rely on the presence of imaging or biomarker evidence and exclude comorbidities are highly selected and do not reflect population settings. **Widely different criteria are applied across AD research. Selection biases in clinic-based studies, case control studies, and clinical trials must be considered when understanding how any specific study's findings relate to the overall picture of dementia in the population**.

In order to improve definition of possible subgroups of people diagnosed with Alzheimer's disease in research, a proposed revision to the amyloid cascade hypothesis [71] suggested three distinct clinical groups, defined by i) the possession of autosomal dominant mutations in familial, early-onset forms of Alzheimer's; and the sporadic forms separated into ii) presence or iii) absence of Apolipoprotein E (*ApoE*) ε4 alleles [71]. While this represents an improvement, with these groups reliably selected on the basis of genotypes, it is still not clear how well these groups reflect the underlying biology of dementia. This definition assumes that all those with genetic mutations will share the same mechanistic pathways, but this is by no means certain, Box 1. For example, mutations in the gene encoding APP can be grouped by how levels of Aβ production are changed, which can be associated with different patterns of amyloid deposition as amyloid plaques or as cerebral amyloid angiopathy (CAA) [72].

GAP 2 - MOLECULAR IDENTITY FOR AMYLOID-BASED BIOMARKERS

Aβ is interpreted as a discrete entity that is easily measured. However, Aβ is derived from APP via a complex series of competing cleavages [73, 74], Fig. 1, first described as a molecular hub, where multiple cellular signalling systems converge, by Turner et al. in 2003 [73]. Figure 1A illustrates just three of the many cleavage pathways of interest. The high level of shared amino acid sequences between full length APP, and its

Box 1. Gap 1 key questions: defining Alzheimer's disease and dementia to support future research strategies

- How can the characteristics of participants in dementia research be characterised in a way that better reflects the likely underlying pathophysiology of their dementia syndromes?
- How do we translate findings from highly selected trial cohorts to actual populations which have, or are at risk of, developing dementia in the community, where the relationships between dementia and neuropathology are more complex and frailty and comorbidity is common?

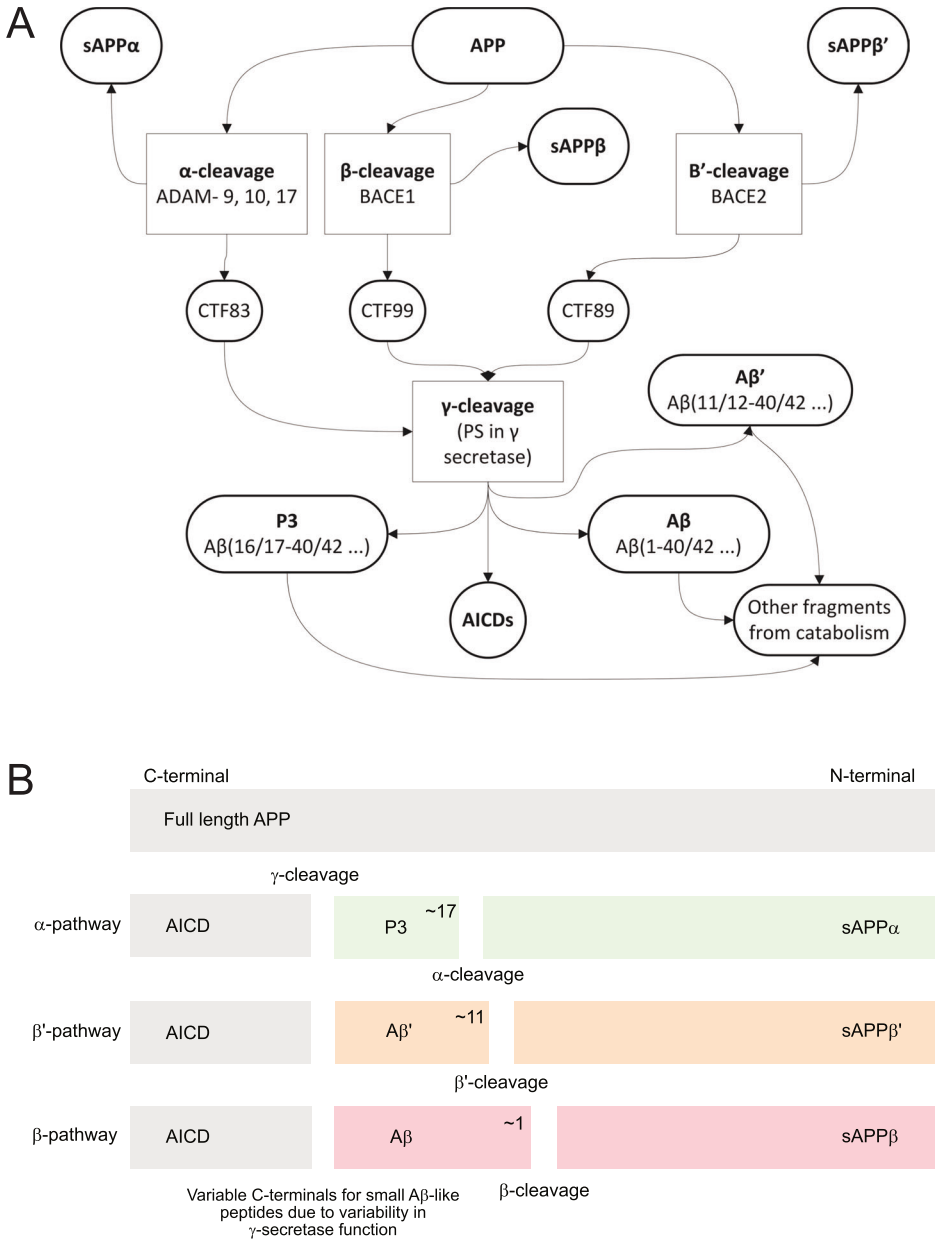

Fig. 1 The correspondence between APP cleavage pathways and proteolytic fragments with shared amino acid sequences. A Flow chart showing three of the many possible cleavage pathways for the amyloid precursor protein (APP) and their associated fragments. The α- Aβ'- and β- cleavage pathways converge on γ- cleavage. CTF carboxy terminal fragment remaining in the membrane after initial cleavages, PS presenilins as part of the γ-secretase complex, AICD APP intracellular domain. P3, Aβ' and Aβ represent the variable length peptides released following γ-cleavage. In the constitutive α-pathway APP is cleaved by a number of enzymes to release a large extracellular protein called soluble amyloid precursor protein α (sAPPα) leaving a membrane bound fragment that can be further processed by γ-cleavage, involving the presenilins, to P3, corresponding to Aβ from amino acid ~17. In the Aβ' pathway, APP is first cleaved by an enzyme called BACE2 to release the large extracellular sAPPβ' and a smaller Aβ' fragment corresponding to Aβ from amino acid 11, In the β-pathway, APP is cleaved by an enzyme called BACE1 to release a large extracellular protein sAPPβ that is ~17 amino acids shorter than sAPPα, leaving a membrane bound fragment that can be further cleaved by the γ-secretase to release Aβ that is ~17 amino acids longer than P3. **B** Diagram showing the substantial sequence homology between the peptide fragments derived from the APP proteolytic system shown in Fig. 1A; fragment lengths are not to scale.

derivatives – the large soluble N-terminal fragments, sAPPα, sAPPβ' and sAPPβ from the α-, β'- and β- pathways respectively and between the smaller fragments from those pathways following γ-cleavage - P3, Aβ' and Aβ is illustrated in Fig. 1B.

Due to variations in cleavage and catabolism, there are over 40 Aβ-like and P3-like peptides that share varying degrees of amino acid sequence [75, 76]. Studies looking at antibody reactivities have shown varying degrees of cross-reactivity for the anti-Aβ antibodies used in research and in clinic across these peptides [77, 78]. The currently favoured antibody for many Aβ studies, 4G8, reacts with an epitope within Aβ18–23 contained in its intended target Aβ, but also in Aβ' and P3 [77, 78]. This is significant; **any study using 4G8 could be measuring output from any/all the α-, β'- and β- cleavage pathways, meaning there is considerable uncertainty about exactly what this antibody is actually measuring**. Many antibodies used to detect the C-terminal residues of Aβ to describe the Aβ42:Aβ40 ratio, a biomarker used in current research and diagnostic practice, also

react with P3–40, P3–42 and others with similar C-terminal amino acid sequences [77, 78]. However, the P3-like and Aβ′ fragments are rarely measured to control for cross reactivities. **Therefore, studies investigating the Aβ42:Aβ40 ratio are potentially measuring changes to P3s and Aβ's as well as Aβ, leading to incorrect interpretations of outputs from the α-, Aβ′ and β-cleavage pathways in experimental settings**. Further uncertainty is introduced by Aβ post translational modifications, peptide solubility and Aβ aggregation state as monomers, dimers, oligomers and fibrils, each of which may react differently with commonly used antibodies.

Work to characterise selected anti-amyloid antibodies that had been used in previous clinical trials [79–81] revealed significant cross reactivities of two of these (Solanezumab and Crenezumab) with a wide range of other proteins, in addition to those derived from the APP proteolytic system and predicted from sequence homology. While antibodies, such as Bapineuzumab and Aducanumab, raised against N-terminal epitopes to recognise species of Aβ, others, such Solanezumab, are less precise and would be predicted to have wider reactivity profiles [1], potentially reacting with species from the α- and β′ pathways in addition to the β-cleavage pathway. Attention in basic biomedical science is again focusing on antibody reactivity profiles following the finding that up to 50% of commercially available antibodies may miss their targets depending on application [82].

Far from being clear cut, the measurement of Aβ is complex and potentially imprecise in terms of both its specific amino acid sequence, solubilities and aggregation state. There is no precise method of measurement to clearly separate each fragment from the 40 + other similar fragments seen. We do not know the precise cross-reactivities of anti-Aβ antibodies with other fragments derived from the APP proteolytic system. **The gaps in our understanding of specific molecular species of Aβ hamper our ability to develop more precise biomarkers and therapeutic agents, to understand exactly what it is they are measuring and exactly what a 'positive' result means at the molecular and clinical levels,** Box 2.

GAP 3 - THE COMPLEXITY OF THE AMYLOID PRECURSOR PROTEOLYTIC SYSTEM

APP is constantly expressed, cleaved and recycled. The amount of the APP expressed in cells can change over time in response to various factors. At any one time, the amount of the APP is rate-limiting [83] and the cleavages compete with one another. This means that if processing of the precursor is directed towards the α-pathway, then less is available for the β-pathway, and vice versa. This is confirmed by those few studies that have measured both Aβ and sAPPα [84, 85]. Further, full-length (i.e. pre-cleavage) APP has functions itself [86]. Therefore, in order to understand what is happening as Aβ production is increased - the main feature of the amyloid cascade hypothesis - we also have to consider gains and losses of function in full-length APP, and all the other fragments [87]. We have previously proposed a framework to model this complexity, the APP matrix approach [72, 74, 87–90], an approach that integrates evidence from wide ranging areas in dementia research, summarised in Fig. 2.

Box 2. Gap 2 key questions: systematic approach to molecular identification

- How do we define Aβ and other fragments from the APP proteolytic system better as separate molecular entities?
- How do we respond as a research community to the significant issues raised by poor antibody characterisation in curating the amyloid evidence base?

Features associated with fragments derived from the various competing cleavage pathways in the APP proteolytic system are often opposing. For example, sAPPα promotes long term potentiation (strengthening of synaptic activity) [91], while Aβ promotes long term depression [92–94] at synapses, and the two cleavage pathways may have opposing roles in programmed cell death [95]. These relationships may in fact indicate the physiological importance of the dynamic balance between the competing α- and β- and other APP cleavage pathways. This would be in keeping with our general understanding of homeostatic mechanisms, that cannot be fully described by measures of just one factor such as Aβ. Some consequences associated with APP proteolysis may be better reflected in ratios of other fragments such as sAPPα:Aβ or P3:Aβ and may depend on which feature is being examined. The different reactivity profiles of the antibodies used for immunotherapy may also modulate these ratios in different ways. Those specific for the N-terminal of Aβ can be expected to increase the sAPPα:Aβ and P3:Aβ ratios, whereas those with wider reactivity profiles may preferentially increase the sAPPα:Aβ and not the P3:Aβ ratio. This is significant because an imbalance between the pathways, in addition to absolute levels of APP proteolytic fragments, could contribute to disease development and progression. **No data for relative rates between the cleavages have been collected to investigate this perspective**.

P3, Aβ′ and many other fragments from the competing APP cleavages have been neglected across dementia research. However, in addition to antibody cross-reactivities, evidence suggests that P3 contributes to Aβ aggregation [96–99], is associated with diffuse amyloid deposition as extracellular cotton wool type amyloid plaques in the brain [100, 101], and that it is deposited with Aβ in blood vessel walls as cerebral amyloid angiopathy (CAA) [102] (perhaps of significance for investigations into haemorrhagic side effects seen in anti-amyloid trials) [11]. **The possibility of competitive binding and mutual antagonistic behaviour between the various fragments from the competing cleavage pathways has received very limited attention in past research strategies, yet this may be a key feature of how the APP proteolytic system functions. The possibility that P3, or indeed any of the other ~ 40 Aβ-like fragments, may act as competitive binding antagonists to Aβ** [87, 89, 90, 103] **has not been tested**.

The complexity of the APP proteolytic system is reflected in a detailed examination of the consequences of disease causing mutations in the *AβPP* gene encoding APP [72]. Mutations associated with the alpha cleavage site increase Aβ, (both Aβ1-40 and Aβ1-42) and the Aβ42:Aβ40 ratio. Those located around *AβPP* codon 693, coding the amino acid 22 in Aβ, have diverse neuropathological and molecular effects that depend on the specific amino acid substitution [72]. Those mutations, located around the gamma secretase (involving the presenilins) site, show similarities with mutations in the presenilins (reduced total Aβ, increased Aβ42 and increased Aβ42:Aβ40 ratio) [72]. The different ways that each mutation changes how Aβ is produced fall neatly around the cleavage sites. The majority of mutations around the α-cleavage site that are associated with dementia can be interpreted as loss of α-cleavage function, with a resultant increase in β-cleavage. In contrast the protective Icelandic mutation (A673T) can be seen as gaining α-cleavage function with follow on loss of β-cleavage. **No studies have systematically investigated the many possible pathways from the APP proteolytic system to dementia in either laboratory-based studies or in the human population. It is not known if other ratios of the various proteolytic fragments e.g. sAPPα:Aβ or P3s:Aβs would be a better biomarkers to describe the APP proteolytic system, and what consequences this might have for participant selection in trials**.

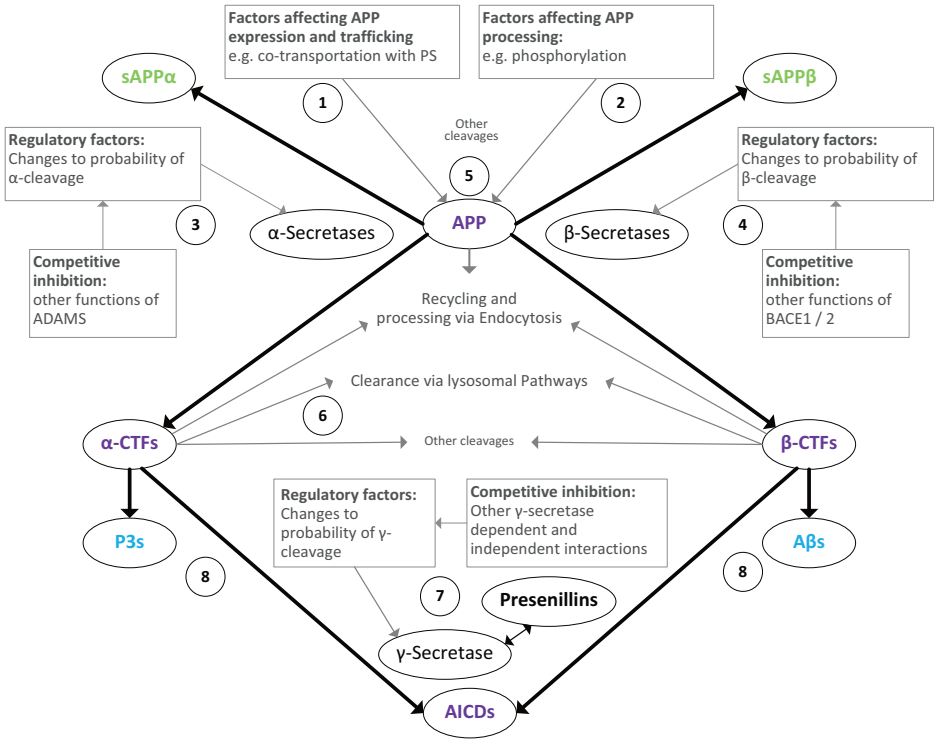

Fig. 2 The APP matrix approach. Adapted from [87]: Green: N-terminal fragments, blue: Aβ and P3 type fragments, purple: other fragments, grey: regulatory factors and processes. 1. Full length APP expression is likely rate limiting both for full length APP functional interactions and APP cleavages; factors that regulate APP expression and trafficking to particular cellular compartments may involve multiple cellular systems. 2. Factors that regulate the likelihood of the various APP cleavages, e.g. phosphorylation of threonine APP668 in the intracellular domain [125] may involve multiple cellular systems. 3. α-cleavage, involving the A Disintegrin And Metalloproteinase (ADAM)s 10, 17 and 9 [126], generates sAPPα and the carboxy terminal fragment (CTF) C83 and is considered to be constitutive and in contrast to β-cleavage appears to include redundancy of multiple enzymes. 4. β-cleavage involving BACE1 generates sAPPβ and the CTF C99 [127]; competitive inhibition arising from other substrates of BACE1 [128] requires clarification. 5. Other cleavages, e.g. by BACE2 [129] and the N-terminal eta-cleavage [130], have been omitted here for clarity but must be included in the full APP matrix approach. 6. Factors regulating processing of particular CTFs in specific cellular compartments require further clarification. 7. Factors regulating the expression, trafficking and functions of PSs [131] either dependent or independent from the γ-secretase complex [132] and competitive inhibition between different γ-secretase substrates e.g. Notch 1 [133] require clarification; while proteolysis of the CTFs C83 and C99 by γ-secretase may be differently affected by γ-secretase inhibitors [134] the relative affinities of γ-secretase with all CTFs have not been fully described. 8. Multiple molecular forms (amino acid sequences, post-translational modifications and aggregation states) have been collapsed into a single node for both Aβ and P3 for clarity but would be required in the full APP matrix. Further processing pathways e.g. via BACE2 [129] and catabolism of fragments e.g. Aβ [135] and CTFs [136] have also been omitted for clarity.

Particular mutations in *AβPP* are also associated with distinct patterns of amyloid in the brain, which is deposited either as plaques in the extracellular space, or in blood vessels (both large and small) as cerebral amyloid angiopathy (CAA). Investigating these different types of amyloid deposition may have particular significance for side effects arising from vascular factors. The consistent deposition of Aβ in blood vessels as CAA, but with few amyloid plaques, seen in those with the Dutch (E693Q) and Italian (E693G) mutations at codon 693 in the *AβPP* gene, suggests that CAA may involve disease-associated pathways that are independent from amyloid plaques [72]. Further neuropathological evidence of two types of CAA in the population, defined by the presence or absence of amyloid deposition in capillaries, also supports the concept of multiple pathways to dementia. There is additional evidence of variability in the range of neuropathological features in those with APP mutations [72], where the Dutch E693Q and Italian E693K mutations are associated with severe CAA, few amyloid plaques and no neurofibrillary tangles, while the Arctic E693G mutation at the same codon is associated with CAA, numerous plaques and neurofibrillary tangles [104].

Research investigating CAA in relation to dementia has been focused mainly on amyloid clearance - as required by the amyloid cascade hypothesis, rather than as a potential independent contributor to disease. Because clinico-pathological studies frequently classify CAA as a vascular pathology, it is often combined with other vascular features in analyses and the contributions of CAA independent from other vascular features are overlooked. Consequently, **pathogenesis of CAA and the source(s) of Aβ deposited in the cerebral vasculature are still uncertain, and represent an urgent research gap**. Brain-derived Aβ may accumulate in vessel walls due to failure of vascular drainage pathways in the brain [105], or via more complex interactions with components of the vasculature [106]. Contributions to Aβ deposition from failure of the glymphatic drainage pathways have also been proposed [107, 108]. Evidence also supports the derivation of Aβ from systemic sources such as blood platelets [109, 110] or smooth muscle cells of the vessel walls [111, 112]. We do not yet have the required evidence to investigate potential differences to disease pathways for Aβ deposited in brain parenchyma as opposed to Aβ deposited as CAA, nor how these differences may contribute to clinical expression of the dementia syndrome, or indeed who may be prone to haemorrhagic side effects in AB immunotherapy trials.

Taken together, the genetic and neuropathological evidence support the likelihood that there are multiple pathways to amyloid deposition that may differ between brain parenchyma and vascular tissue types. A more nuanced research strategy to

Box 3. Gap 3 key questions: Characterising the contributions of Aβ in the context of the APP proteolytic system

- How are the contributions of the APP proteolytic system best described, examined and understood?
- Which ratio(s) of fragments from the APP proteolytic system best represents its function?
- Can we define a standard battery of APP protein fragments to report against when presenting research and developing new biomarkers?

Box 4. Gap 4 key questions: placing the APP proteolytic system in context of the cellular milieu

- What are the contributions of the APP proteolytic system to normal function and dementia, and are these the same across tissue types?
- How do we best investigate the dynamic feedback interactions between the APP system and other systems from the wider cellular milieu over different time periods?
- Will one therapeutic intervention be enough considering all the cellular and physiological systems involved in neurodegeneration?

understanding amyloid deposition is required to tease apart the relationships between specific mutations, neuropathological expression, and clinical dementia status, Box 3.

GAP 4 PLACING THE AMYLOID PRECURSOR PROTEIN AND ITS FRAGMENTS IN THEIR PHYSIOLOGICAL CONTEXT

The research that has been completed on the APP system has focused almost entirely on understanding the pathological effects of Aβ. The physiological roles associated with the wider APP proteolytic system and all its fragments are essential, but neglected, areas of this research field. Amongst others, these include roles in oxidative homeostasis [113], inflammation and immune functions, ApoE and cholesterol homeostasis [114–116], regulation of metal ions [117, 118], synaptic plasticity and APP as a regulatory hub [73]. All of these are related to essential cellular functions that potentially contribute to the regulation of APP proteolysis via positive and negative feedback loops within the cellular milieu. There is an urgent need to understand how wider cellular milieu contribute to mechanistic pathways to dementia.

The complexity of the relationships between *ApoE* alleles and Aβ with respect to dementia illustrates the potential wide ranging effects of interactions between two complex cellular systems [119, 120]. While possession of the *ApoE ε4* allele increases risk of developing sporadic dementia, most carriers will not develop dementia in their lifetimes [121]. *ApoE ε4* carriers may also be at higher risk of developing ARIA – E in clinical trials [122]. Beyond its known interactions with Aβ, ApoE has roles in diverse areas including the vasculature, lipid homeostasis, immune system functions and modulation of the contributions of both Aβ and tau to neurodegeneration [114, 115, 119, 120]. The importance of the contributions of ApoE to dementia has been highlighted recently by delayed cognitive decline in an individual possessing both a *PSEN1* mutation, and homozygous for the rare *ApoE* Christchurch mutation, showing reduced tau and increased amyloid pathologies [123, 124]. A systematic approach is required to clarify these effects and how they relate to dementia in the population.

As a hub [73] with complex feedback loops over short and longer timescales [74, 88–90], the APP proteolytic system can be predicted to contribute to maintaining homeostatic points in normal cellular function and contribute to reprogramming of those homeostatic points in disease states where flow through the APP proteolytic system is changed. **To date, few of the interactions between APP and wider cellular systems have been investigated to the detail required to fully understand how they might contribute to normal function, disease state and the side effects seen with the current anti-amyloid drugs, and how we might compensate for changes,** Box 4.

DISCUSSION: WAYS FORWARD TO ADDRESS THESE GAPS

With the new, broader approaches to dementia research strategy shifting research focus to include consideration of a wider range of factors contributing to dementia, it is now time to reflect upon the evidence base we have and the need to refine research strategy within the dementia research community. We have identified several gaps in the current knowledge base that impact significantly on the future of dementia research and suggest alternative perspectives to address these gaps.

The issues of dementia disease definitions and suggested groupings of familial and sporadic dementia syndromes are not easy to tease apart but, importantly, these issues are at the core of the selection problem. Until we have a better way of translating findings between familial, clinical trial and population studies, there will be uncertainty regarding which dementia is being investigated out of the wide-ranging dementia syndrome. Biomedical research that aims to develop therapeutic interventions by using highly selective cohorts is unlikely to be relevant to the real-world experience of the dementia syndrome in the older population.

Quantitative biomarkers such as Aβ, whether measured in CSF, plasma or with imaging, involve binary thresholds that do not reliably define dementia for an individual in the population at any disease stage. While the probabilistic amyloid hypothesis [71] goes some way to solving the problem of imprecise selection based solely on quantitative thresholds by defining disease groups based on genetic factors, this approach assumes that all the autosomal dominant mutations share pathways in common and still doesn't account for the whole APP proteolytic system in normal and abnormal function states. In contrast, we propose that each of these mutations provide for reliable and consistent participant selection and experimentally would be akin to examining knock-in and knock-out laboratory models. We therefore suggest that familial autosomal dominant mutations are categorised first by protein affected then by specific cleavage pathway and then by gains and losses of function. This systematic characterisation from familial forms of dementia could then be investigated in the older population by comparing measures of exactly the same fragments seen in brains from those in the population both with and without dementia. Translation of findings between those with autosomal dominant mutations and those with sporadic disease would rely on a systematic and detailed characterisation of all fragments from the APP proteolytic system and their various relationships with dementia – in effect forming a molecular translational language that can be compared across all Alzheimer-type dementia.

Antibody cross-reactivities in reliable identification of the specific type and form of each fragment derived from the APP proteolytic system affect all proteolytic fragments derived from the APP proteolytic system. Much work remains to exactly define these in fully characterised and transparently described experimental settings. All antibodies should have clear evidence of what they do and do not react with so that it is possible to interpret results without making assumptions. This may be the best starting point to clarify the basic science before further investigations into the APP proteolytic system as a whole. An examination of previous findings in dementia research taking these cross-reactivities into account could identify new areas of research.

APP is part of a complex physiological proteolytic system and its roles in normal and abnormal functions are not well understood. Detailed and systematic investigations of the whole APP proteolytic system, and all its fragments, in relation to dementia

in global population-based studies would yield more reliable biomarkers, and allow future therapeutic trials will be able to select participants with greater confidence. Better characterisation of the APP proteolytic system in the human population will allow description of baselines that could contribute vital data to supporting the direct translation of findings from biomedical studies and therapeutic trials to the population more generally. A better understanding of these pathophysiological amyloid processes has the potential to improve selection of those at greater risk of serious vascular side effects in amyloid immunotherapy trials and to enhance efforts to produce therapeutic agents with more favourable safety profiles. This 'precision medicine' approach should improve trials that add to the evidence base on giving the right therapy to the right patient at the right time with the right monitoring.

The interactions between the APP proteolytic system and the wider cellular environment raise further issues of complexity through regulation of cleavages and feedback loops that control cleavages over time. Little work has focused on understanding these complex relationships over short and longer periods of time. Research strategies should be designed that include and reflect this multifactorial complexity of the dementia syndrome, to place the amyloid precursor protein proteolytic system and all of its fragments in their physiological context. Better characterisation of these wider ranging features of brain ageing in the older population will enable better translation between biomedical studies, clinical trials, and the population.

CONCLUSION

In this contribution we argue with compelling evidence that there are significant gaps in our biological understanding which remain to be addressed. A period of intense study is required to ensure the best outcome from current investments into research into the mechanisms contributing to the clinical dementia syndrome also creating a far more robust evidence base. Systematically addressing these knowledge gaps will take time. Moving towards a cross-disciplinary approach to dementia research with an appropriate framework to integrate evidence from different research perspectives, will enable us to answer long-standing biological questions that the field must address urgently as it moves into a new era. Addressing these gaps will give us the platform to make true progress, leading to widespread, meaningful improvements to the experience of those living with dementia that has eluded the field for so long.

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AUTHOR CONTRIBUTIONS

SH wrote the paper in discussion with SW and CB. All authors contributed to drafting and final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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